Applicants appreciate the acceptance of the new Declaration as well as the withdrawal of the rejections under 35 U.S.C § 103 and the rejections for double patenting. Applicants also appreciate the withdrawal of the rejections under 35 U.S.C. § 112, ¶ 1 related to transgene expression.

A. Rejection Under 35 U.S.C. § 112, ¶ 1

The Office Action dated December 10, 2001, rejected claims 1-19 and 21-24 under 35 U.S.C. § 112, ¶ 1, for allegedly not being enabled for "a transgenic, non-human mammal comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said non-human mammal."

First applicants appreciate the acknowledgment by the Examiner that the specification is enabled for a 1) "transgenic mouse whose genome comprises a human LCR γ-β hemoglobin switching DNA construct, wherein said genome is further homozygous for murine α- and β-globin knockout alleles such that said knockout alleles result in said mouse failing to synthesize murine hemoglobin, and wherein said hemoglobin switching construct is expressed such [that] said mouse develops hemolytic anemia." and 2) that the expression of the α- and β- globin transgenes is enabled. Thus, as Applicants understand the remaining area of difference between the PTO and the applicant, with respect to enablement, as based on two issues 1) the necessity of proven successful ES technology for animals other than mouse, and 2) that switching construct technology is required for all animals to enable the claimed subject matter. Each of these issues is addressed below.

Applicants have provided a copy of Dr. Townes' declarations, the Townes Declaration 1 and Townes Declaration 2, for the Examiner's convenience, as the statements set forth in those declarations are still applicable to the enablement of the present claims, and Applicants refer to them herein. As a reminder, the Townes Declaration 1 sets forth that which was known by the skilled artisan at the time of the application with respect to making the claimed non-human mammals and concludes that the skilled artisan was enabled to make non-mouse mammals as claimed, based on the specification and that which was known in the art at the time of the

application. The Townes Declaration 2 sets forth that a switching construct is not necessary for a general hemoglobin transgene.

*1. **Specification enabled for making non-mouse mammals***

Applicants understand the position of the Examiner to be that the specification is not enabled for making non-human mammals as claimed because 1) "the examiner does not agree that the art at the time of filing teaches the production of mammals by nuclear transfer of *modified nuclei*" (Office Action at page 4, emphasis added), 2) the art of nuclear transfer is unpredictable and thus not enabling, and 3) the "Applicant has not provided any evidence that these other mammalian putative ES cells were shown to be totipotent." (Office Action at page 5). Arguments 1 and 2 are directed at Applicants' assertion that nuclear transfer technology enables the present claims and argument 3 is directed at Applicants' assertion that ES cell technology did exist for animals other than mouse at the time of the application. It is important to note that if either nuclear transfer technology **or** ES cell technology are enabled then the rejection should be removed. Each of these arguments is addressed below.

a) The art at the time of filing does enable nuclear transfer for modified cells

The Examiner argues that Campbell et al., Biology of Reproduction, 50:1385-1393 ("Campbell") and Campbell et al. "Live lambs by nuclear transfer from an established cell line," Theriogenology, Vol. 45(1):287-287 (January, 1996) ("Wilmut Abstract") do not teach the use of nuclear transfer technology *along with modified cells*. While it is true that the cells manipulated by the researchers in Campbell and the Wilmut Abstract do not use genetically modified cells it is not true that the Campbell and Wilmut Abstract did not envision using their methods with genetically modified cells.

For example, the first sentence of the Wilmut Abstract states, "The ability to clone mammalian species from an established cultured cell line would confer innumerable advantages in the field of animal biotechnology." Surely, the Examiner does not believe that the "innumerable advantages" recited by Campbell et al. in the Wilmut Abstract did not include the knowledge that cultured cells allowed the manipulation and creation of embryos from nuclei which had undergone transgenesis. From the first experiments performed in mouse in the mid

80's by Sedivy and co-workers, it was understood that blastocyst formation from cultured cells was beneficial for use in transgenesis and specifically knockout technology thrived using cultured cells for nuclear transfer or chimera formation.

In so far as the Examiner's argument depends on the need for a reference indicating that the knowledge to perform nuclear transfer with modified cells required the suggestion to perform this type of animal production, the Examiner is respectfully directed to the art of record, provided by the PTO. For example, in Seamark, "Progress and Emerging Problems in Livestock Transgenesis: a Summary Perspective," Reprod. Fertil. Dev. 6:653-7 (1994) ("Seamark"), the entire article is about "transgenesis," i.e. making genetically modified animals through the introduction of non-native nucleic acid into the animal. Large sections of the Seamark article deal with the advances of ES technology in making "transgenic animals," as well as the use of the "nuclear transfer" to produce transgenic animals. It was widely understood at the time of Campbell and the Wilmut Abstract that transgenic animals were facilitated by the use of both ES technology and by nuclear transfer technology.

Thus, it appears to Applicants that the Examiner's position is that nuclear transfer was enabled for mammals, but that it had not been shown at the time of the priority application that transgenesis could be practiced in conjunction with the enabled nuclear transfer technology. As has been discussed before, the field of transgenesis was very mature at the time of the present application, especially in the field of erythrocyte transgene expression. The Examiner has provided no evidence to indicate that transgenesis would alter the methods of nuclear transfer fully enabled and practiced at the time of the priority application. Applicants believe, as likely the Examiner does as well, that *the methods of transgenesis*, do not alter *the methods of nuclear transfer*. In other words, the methods practiced for "non-modified nucleus" nuclear transfer techniques are the same as the methods for "transgenic modified nucleus" nuclear transfer techniques. They do not appreciably differ. What was enabling for non-modified nuclei was and remains today, enabling for modified nuclei. Westhusin, et al., Theriogenology 55:35-49 (2001) cited in the Office Action supports this position (page 44, third full paragraph). Westhusin clearly indicates that the same methods used for cloning non-modified cells work for modified cells, albeit at a lower cloning efficiency per cell. Pennisi supports this same position. Pennisi

states when referring to the addition of foreign genetic material into a sheep by Campbell, shortly after the Campbell publications discussed herein, "It didn't take much work to add new DNA to the cultured fetal cells, select those that tool in the new genes, and fuse them with enucleated eggs. It worked as evidenced by the birth of Polly and five other lambs bearing the gene for human factor IX, published in December 1997." Futhermore, Pennisi discusses the 1999 success by David Ayares and co-workers in showing that knockout technology could be practiced with nuclear transfer technology, essentially as described in 1996 in the Wilmut Abstract, mere increases in efficiency being achieved. As discussed below, efficiency, however, does not determine whether experimentation is undue.

Applicants' burden requires that a method, which works, exist at the time of the priority application, not that the method *was shown* to work in all of its manifestations at the time of the priority application. Campbell, the Wilmut Abstract, the art relied on by the PTO, and most importantly the declarations provided by Dr. Townes, the Townes Declaration 1 and Townes Declaration 2, indicate that what was enabling at the time of the priority application remains enabling today. Applicants in the present application showed that a mammal could survive completely on hemoglobin from another species, i.e. its endogenous hemoglobin could be completely substituted with that of another species. The invention lies not in the *making* of the knockout animals, but in showing that the disclosed knockout animals live. It remains a fact that the pioneering work by the applicants would be practiced as disclosed in the application for any mammalian species. Applicants showed that an animal *survives* on another animal's hemoglobin. Applicants *have made* an animal that lives on another animal's hemoglobin. As shown in the application and in the art at the time of the application the skilled artisans held in their hands, literally, the necessary tools and recombinant methods needed to make the claimed animals. Once applicants showed that the animals could be made, the full power of the existing technology ment that any mammal could be made that lacked its endogenous hemoglobin, surviving on another species hemoglobin . . . even if those methods had not been physically made or the nuclear transfer and ES methods had not been shown to work for all mammals.

b) Low cloning efficiency does not mean unpredictable as it relates to undue experimentation

In conjunction with the Examiner's position that Applicants have not physically shown that the animals have been produced, on page 5-7 of the Office Action, the Examiner argues that Campbell and the Wilmut Abstract, as well as other references cited by the Examiner, indicate that the field of ES technology and nuclear transfer technology were unpredictable. According to the PTO this alleged unpredictability creates undue experimentation in practicing the claimed subject matter. The Examiner relies on three references, Westhusin et al., Theriogenology, 55:35-49 (2000), Polejaeva et al., Nature, 407:86-90 (2000), and Pennisi and Vogel, Science, 288:1722-1727 (2000) for support of this point. It is true that these three references indicate that the efficiency of cloning a particular cell or a particular animal is low, at 1-2% (see Polejaeva, page 86). But it is just as true, as agreed by the Examiner, that these three references have shown that the basic methods set forth by Campbell and the Wilmut Abstract worked for many different mammals, including sheep, cattle, mice, and goats. Polejaeva states, "The methodology used for embryo reconstruction in each of these species is essentially similar: diploid donor nuclei have been transplanted, into enucleated MII oocytes that are activated on, or after transfer." Polejaeva at 86. Westhusin states, "Cloned sheep, cattle, goats, pigs, and mice have now been produced using somatic cells for nuclear transplantation." Westhusin at 35. Pennisi states, "Cumulina, Cupid, Peter, Webster, Diana, Dotcom, Dolly. Once the realm of science fiction, cloned animals are now becoming almost *common place*." Pennisi at 1722 (emphasis added). Surely "common place" is far more predictability than is needed to meet the undue experimentation burden imposed by the courts, and should in fact be enough to meet the increased burden placed on the Applicant by the PTO.

As will be discussed more below, after a discussion of the enablement standard as it applies to "efficiency" is provided, Westhusin, Pennisi, and Polejaeva each support Applicants' assertion, put forth in Townes Declaration 1: The methods and knowledge needed to make cloned animals existed at the time of the present application, and therefore enabled the skilled artisan to practice the claimed subject matter. It is axiomatic that "undue experimentation" is viewed through the lens of the given technology, thus, different amounts of experimentation can be performed without being undue for different technologies. The presently claimed subject

matter and corresponding enablement parallel existing case law very well, and just as the Federal Circuit held the technology in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) to be enabled, so to Applicants believe the PTO will find the presently claimed subject matter enabled.

(1) Enablement standard

The standard for determining whether claimed subject matter would take undue experimentation to practice the claimed subject matter is set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976).

(a) Undue experimentation is art specific

The facts underlying the decision of *In re Wands*, the benchmark case on enablement, illustrate well the concepts put forth in *MIT v. A.B. Fortia* and *In re Angstadt.* The method claims at issue in *Wands* involved the use of an antibody wherein the "antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for . . . [the antigen] of at least 10^9M^{-1}." *In re Wands*, 858 F.2d at 734. This claim covers *any* monoclonal antibody, not just a specific monoclonal antibody, and the PTO argued that the Applicant failed to enable *all* monoclonal antibodies. *Id.* Briefly, the skilled artisan generates monoclonal antibodies by injecting an antigen into a host animal causing an immune reaction, isolating spleen cells, some of which produce the antibodies that bind the antigen, fusing the spleen cells with a cancerous myeloma cell producing a hybridoma, and then screening individual hybridomas to isolate those that produce antibodies that bind the antigen. *Id.* at 733-734. The PTO supported its non-enablement position by pointing out that 1) not all hybridomas produce antibodies that bind antigen, 2) not all hybridomas that bind antigen will bind with an affinity of 10^9M^{-1}, and 3) the Applicants own data indicated that a small percentage of hybridomas actually produced monoclonal antibodies which fell within the scope of the claims. *Id.* at 738-739. The court rejected these arguments by stating,

> cell fusion [hybridoma technology] is a technique that is well known to those of skill in the monoclonal antibody art, . . .[t]here was a high level of skill in the art at the time when the application was filed, and all the methods needed to practice the invention were well known . . . [and] it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened, . . .[and since] Wands . . . was successful . . . in making at least one antibody that satisfied all of the claim limitations . . . Wands evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.

Id. at 740. Furthermore, the Wands court made clear that the amount of and type of experimentation considered undue fluctuates for each type of art. *Id.* The quantity of experimentation lacks relevance outside an assessment of what is "routine experimentation" in the art. *Id.* Thus, the huge amount of "experimentation" that the skilled artisan would have to perform to practice Wands' invention: immunizing an animal, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the hybridomas for the desired characteristics, *knowing that many hybridomas would not produce functional antibodies and* ***not*** *knowing which hybridomas would produced claimed antibody*, was not undue experimentation because it was routine experimentation in the art of monoclonal antibody production. *Id.* As discussed below, the present claims and corresponding enablement rejection closely parallel the situation presented in *Wands* since the art of producing the presently claimed non-human mammals expressing the disclosed constructs is routine experimentation in the art of non-human mammal transgenic production even though it may seem complex.

(b) Enabled for the Skilled artisan at the filing date

An application must be read through the eyes of the person of ordinary skill in the art[1] and information known to one of ordinary skill in the art may be relied upon for purposes of the

[1] "Patents . . . are written to enable those skilled in the art to practice the invention, not the public." *W.L. Gore & Assoc., Inc. V. Garlock, Inc.* 721 F.2d 1540, 1556 (Fed. Cir. 1983) (citing *In re Stores*, 245 F.2d 474, 478 (CCPA 1957))

enablement analysis. *In re Glass*, 492 F.2d 1228, 1232 (Fed. Cir. 1974).[2] A patent application preferably omits that which is well-known or common knowledge to those of ordinary skill in the art.[3] Thus, an applicant should not be penalized for leaving out information in his patent application that those of ordinary skill in the art knew or could readily have obtained at the time of the filing of the patent application. The specification must be enabled at the time of filing the application. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993).

(c) The skilled artisan knows that which is available

The skilled artisan knows the fundamental knowledge specific to the particular art and the places and ways to search out particularized information. *In re Howarth*, 654 F.2d 103 (C.C.P.A. 1981). Thus, English publications and US patents are part of the skilled artisans knowledge.

(2) The art of nuclear transfer and ES technology works has indicated an inefficiencies do not cause undue experimentation

Just as in *Wands*, at the time of the present application, methods existed that could be used to produce the claimed mammals. While they may not have already been used to produce the claimed mammals, the techniques of nuclear transfer and the experimentation needed to perfect them existed at the time of the present application. The passing of time revealed that the basic concepts of nuclear transfer, set forth by Campbell and the Wilmut Abstract, have proven true for many mammalian species, including bovines (This was acknowledged by the Examiner on page 6 of the Office Action, as indicated by Westhusin).

The art of nuclear transfer and ES technology involves substantial and complex manipulations, but this does not mean that the manipulations constitute undue experimentation. The experimentation needed to practice nuclear transfer technology, in mammals, is not

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[2] See also *In re Mott* 539 F.2d 1291, 1296 (Fed. Cir. 1976) stating, "The evidence upon which appellant may rely to show what meaning persons skilled in the art would attribute to his disclosure for the purposes of § 112 and § 132 is that which pertains to the *public* knowledge extant on appellant's effective filing date." (emphasis in original).

[3] "[A] . . . specification need not disclose what is well known in the art." (*Lindemann Maschinenfabrik v. Am. Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984) (citing *In re Myers*, 410 F.2d 420 (CCPA 1969). See also *Hybritech Inc. v. Monoclonal Antibodies, Inc.*802 F.2d 1367, 1384 (Fed. Cir. 1986).

considered undue, just as in *Wands*, the incredible amount of screening necessary to find the claimed antibodies was not considered undue because that it is how the art of antibodies was practiced. Likewise with the art of cloning, nuclear transfer technology, after the publication of Campbell and the Wilmut Abstract, was understood by those of skill in the art to indicate that nuclear transfer would work for mammals, including sheep. As Dr. Townes stated,

> As of January 1996, methods for culturing cells which could be successfully used in nuclear transfer experiments were known to those producing whole animals from cultured cells. To be able to perform nuclear transfer a researcher needs to know the conditions under which the donor nucleus is propagated, the conditions under which the recipient oocyte is maintained, and the conditions for transferring the donor nucleus to the recipient oocyte. Campbell et al., (Exhibit 1) along with the Wilmut Abstract (Exhibit 2) teach all three of these conditions for nuclear transfer of cultured cells.

Townes Declaration 1, paragraph 8. Campbell and the Wilmut Abstract taught what was necessary to produce the claimed non-human mammals, without undue experimentation, as this is set forth in *Wands*. Optimization of these conditions, subsequent to Campbell and Wilmut's contribution, does not make the use of their method undue experimentation.

Westhusin, Polejaeva, and Pennisi, as indicated above support this position. Westhusin, Polejaeva, and Pennisi, all support that the basic steps of nuclear transfer were outline in 1995, and that while the efficiency of cloning any given animal or species can vary and is typically low, the same basic steps work today that worked back when the method discussed in the Campbell and Wilmut Abstract was performed. Just as a 2-3% success rate was not dispositive on the enablement question in the art of making monoclonal antibodies, so too a 1-2% success rate should not be dispositive on the enablement question in the art of making cloned animals. Just as in *Wands*, what should be focused on, and dispositive, is that there is a *predictable* percentage that will always be produced. Even if the percentage is low, cloned animals can . . . and will . . . be produced. The effort it takes to get the cloned animal is unique to the art of cloning, and does not impact the undue experimentation analysis, just as it did not impact the undue experimentation analysis in *Wands*.

Therefore, a rejection under 35 U.S.C. § 112, ¶ 1 of claims 1-19, and 20-24 based on the inability to make the knockouts of the alpha and beta globin genes in mammals other than mouse because of inability to practice nuclear transfer techniques with modified cultured cells is respectfully traversed, and reconsideration of the claims is requested. Thus, on this basis the rejection under 35 U.S.C 112 should be removed.

c) Applicant need not provide evidence of germline transmission

The claims are also separately enabled because ES cells can be used to produce the animal. In this regard, the second general argument put forth by the Examiner arises from the assertion that germ line transfer of the various non-murine mammalian ES cell lines discussed in the numerous publications relied on by the PTO had not been shown, and therefore the cell lines were not enabling for the presently claimed technology. First, this applies an incorrect standard for enablement to the Applicants' claimed subject matter, and second, not withstanding this incorrect standard, the ES cell lines are considered totipotent.

Applicants are not required to show that the putative cell lines were in fact totipotent. What remains true is that the Examiner has indicated that ES lines for mammals did not exist at the time of the present application. Contrary to the position of the PTO, the publications of record clearly indicate otherwise. The ES cells were referred to as putative, not because they questioned whether they would some day be shown to be totipotent, but merely because they hadn't been so shown. Importantly the claims do not require that any animal ever be produced that have germline transmission. The claims merely require that an animal be produced. Germline transmission would be required to mate animals having the desired phenotypes, but it would not be required to produce an animal that has the claimed characteristics. Furthermore, notwithstanding the above, it is undisputed that today, ES lines exist for animals such as humans.

Just as discussed above, for nuclear transfer technology and cloning, it is clear that germ line transmission of ES cells has occurred or would occur using the same basic blue prints set out at the time of the present application. Furthermore, a key point to remember is that in 1994, 1995, and 1996, the emphasis and effort of the research community to reproduce results which made cloning a reality in mammals other than mice shifted from expanding ES technology to nuclear transfer technology. The burden placed on the Applicants to show that the ES cell lines

available in 1996 were actually shown to produce germline transfer in 1996 is an unfair burden. This showing is not necessary to enable ES cells, as determined by the PTO's own allowance of reported human ES cells and primate ES cells during the prosecution history of United States Patents 6,200,806 and 5,843,780 for "Primate embryonic stem cells" to Thomson. During the prosecution of 6,200,806, the PTO asserted that the claims to human ES cells could not be enabled because germline transmission was not shown. These claims were subsequently allowed without such a showing, indicating that ES cell existence according to the PTO can apparently be enabled without showing germline transmission. Thus, the ES cell lines discussed in Moreadith et al. "Gene Targeting in Embryonic Stem Cells: the new physiology and metabolism," J. Mol. Med. 75:208-216 (1997) ("Moreadith"), Seamark, "Progress and Emerging Problems in Livestock Transgenesis: a Summary Perspective," Reprod.Fertil. Dev. 6:653-7 (1994) ("Seamark"), and Mullins and Mullins, "Perspective Series: Molecular Medicine in Genetically Engineered Animals Transgenesis in the Rat and Larger Mammals," J. Clin. Invest., 98(11) S37-S40 (1996) ("Mullins") should not be held to a higher standard. Therefore, the ES cell lines described at the time of the present application are sufficient to meet the enablement standard for the presently claimed subject matter.

Therefore, a rejection under 35 U.S.C. § 112, ¶ 1 of claims 1-19, and 20-24 based on the inability to make the knockouts of the alpha and beta globin genes in mammals other than mouse because of a lack of showing germline transfer of known art discussed ES cell line is respectfully traversed, and reconsideration of the claims is requested on both this basis as well as on the basis of enablement using nuclear transfer discussed above.

2. Specification enables switching and non-switching constructs

Applicants understand the current position of the PTO on the rejection related to switching constructs to be that a switching construct is not enabled for the full breadth of the claims. As indicated before, first, the full scope of the claims for any transgene is enabled because a switching construct is not needed, but in those rare instances where the expressed hemoglobin is a sickle hemoglobin, or possibly some other type of mutant lower activity hemoglobin. In these situations, as the application indicates, a switching construct can be used,

and was used successfully. Thus, a switching construct is not needed in most cases, and when it is preferred, it has been shown to work, and thus, can be used.

It is understood that Applicants have attempted to summarize the issues put forth by the Examiner. Should this response be insufficient to gain allowance, Applicants reserve the right to address each individual point made by the Examiner, and Applicants' summary should not be viewed as an acquiescence to individual points raised by the Examiner.

The rejection for lack of enablement on this ground is respectfully traversed and reconsideration of claims 1-9 and 21-24 is respectfully requested.

No additional fees are believed due, however, the Commissioner is hereby authorized to change any additional fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence and anything indicated as attached or enclosed is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Box RCE, Washington, D.C. 20231, on the date shown below.

David E. Huizenga — December 4, 2002
Date